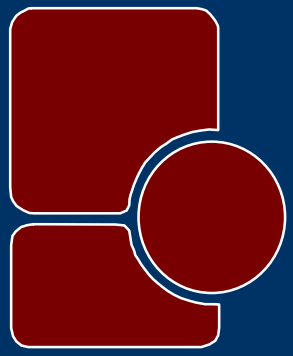
Joint Legislative Audit and Review Commission
of the Virginia General Assembly



Indigent Participation in Medical Research at Virginia's Medical Schools

Staff Briefing
June 11, 2001

Introduction

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Presentation Outline

- ☑ **Study Overview and Summary of Findings**
- ☐ Overview of Human Subjects Participating in Medical Research
- ☐ Indigent Care and Medical Research at Virginia's Medical Schools
- ☐ External Reviews of the Medical Schools for Human Subject Protections
- ☐ Institutional Review Board Funding and Activities
- ☐ JLARC Review of Selected Medical Research Studies

Study Request

- The Commission held a series of planning meetings in September, October, and November 2000.
- As a result of these meetings, the Commission selected six topics for review by JLARC at its November 2000 meeting.
- One topic selected was the review of indigent participation in medical research at Virginia's three teaching hospitals.

Research Activities

- Structured Interviews
  - University officials, institutional review board members and staff, and study researchers
  - Federal agency staff responsible for human research protection
- Review of university research funding, and institutional review board activities, workload, staffing, and funding
- Review of various national and university-level human subject research documents

Research Activities
(continued)

- Site visits to review medical research studies
  - Purpose was to determine, at the study level, whether adequate protections exist for all participants, including vulnerable or indigent persons
  - Reviewed 15 studies with 727 study participants
  - Reviewed regulatory documents and interviewed study staff
  - Individually reviewed consent forms for 342 study participants for compliance with federal regulations, and collected basic demographic information (age, sex, race, and health insurance)

Summary of Findings

- Virginia has three medical schools, which account for most of the health care provided to indigents and most of the medical research conducted - - Virginia Commonwealth University (VCU), University of Virginia (UVA), and Eastern Virginia Medical School (EVMS). All three schools have national reputations in conducting research.
- In recent years, there have been heightened concerns at the national level about the adequacy of protections that are provided to human subjects in research studies.
- In Virginia, there is no evidence at this time that a lack of protections has led to physical harm, but compliance problems with federal regulations led to the temporary suspension of 12 studies at UVA in 1994 and of 1,563 studies at VCU in 1999.

Summary of Findings
(continued)

- The recent federal suspension of all human subject research activities at VCU provides an example of what can happen to a school when the internal oversight function is flawed.
  - For a time, VCU's ability to conduct critical medical research and compete for research dollars was diminished.
  - VCU compounded its own problems with the oversight function by not promptly acknowledging these problems and responding with requested corrective action plans – contributing to the ultimate suspension of all human subject research.

Summary of Findings
(continued)

- As the result of their own initiatives and the suspension of research at VCU, all three schools have made important changes to oversight procedures for medical research. However, further improvements in identifying and protecting potentially vulnerable groups, such as children, minorities, and low-income persons, are still needed and can be accomplished through:
  - Periodic onsite audits of selected medical research studies to ensure compliance with regulations, including the verification of the voluntary nature of participation by study subjects, and
  - The collection of basic, aggregated demographic data on study participants and the identification of potentially vulnerable populations.

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Protection of Human Subjects Participating in Medical Research

- In Virginia, there are three major schools that conduct medical research: Virginia Commonwealth University (VCU), the University of Virginia (UVA), and Eastern Virginia Medical School (EVMS).
- Medical research, often called clinical trials, involves studies to determine the effectiveness and safety of drugs, therapies, or medical devices for use by people.
- The conduct of medical research in this country is under increased scrutiny after several recent incidents at top universities in which the safety of clinical trial participants was compromised.
- The national dialogue on the conduct of medical research is not specifically focused on the abuse of indigent patients or other potentially vulnerable groups. Rather, more scrutiny is being given to the procedures of the institutional review boards (IRBs) and research investigators at the universities who are charged with protecting the safety of all people who enroll in medical research studies.

The Belmont Report Identifies Three Principles for Human Subject Protection

- ***Respect for persons***: **Individuals should be treated as independent decision makers, and should be provided with enough information to make an informed decision about study participation.**
- ***Beneficence***: **Researchers must ensure the well-being of all study participants by maximizing the possible benefits and minimizing the possible harms of the research process.**
- ***Justice***: **Individuals should receive an equitable distribution of both the research burdens and benefits (for example, the inclusion and exclusion criteria in the selection of research subjects should be fair).**
- **Human subject protections are enforced by two federal agencies: the Office for Human Research Protection (OHRP) and the Food and Drug Administration (FDA)**

Federal Regulations Require Three Levels of Protection Mechanisms

- First, there is federal oversight and its requirement that all research institutions contractually agree to comply with federal regulations on human subject protection.
- Second, there is university oversight, which is accomplished through institutional review boards (or IRBs) that review and approve all human subject research studies.
- Third, there is study-level oversight; the study investigator is required to guarantee that all study participants have been given key facts about the study to ensure that their consent is informed and voluntary.

Federal Efforts Underway to Improve Research Involving Human Subjects

- The federal government contributes more than half of all the academic research funding received by institutions across the country. Because of this, the federal agencies have considerable leverage in determining how human subject protections will be implemented.

- The Department of Health and Human Services (DHHS) is implementing several initiatives to improve human subject research. DHHS plans to:
  - improve education and training;
  - issue additional guidelines on consent, including the expectation that this process should be audited;
  - issue new monitoring and conflict of interest guidelines; and
  - pursue legislation to levy fines for violations of informed consent and other federal regulations.

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VCU and UVA Are the Main Providers of Health Care to Indigent Persons

- In Virginia, VCU, UVA, and EVMS are the three major medical schools that provide most of the health care to the indigent population.
- In 1999, VCU alone provided 31 percent of all charity care provided in Virginia.
- VCU and UVA together provided the majority of Medicaid-funded inpatient and outpatient hospital care.
- Sentara Hospital, which is part of the EVMS network of hospitals, is one of the top five hospitals in dollars of charity care provided in the State, even though its overall percentage is less than five percent.

Health Care Provided to Indigent Persons by Virginia's Medical Schools in 1999

(In Millions of Dollars)

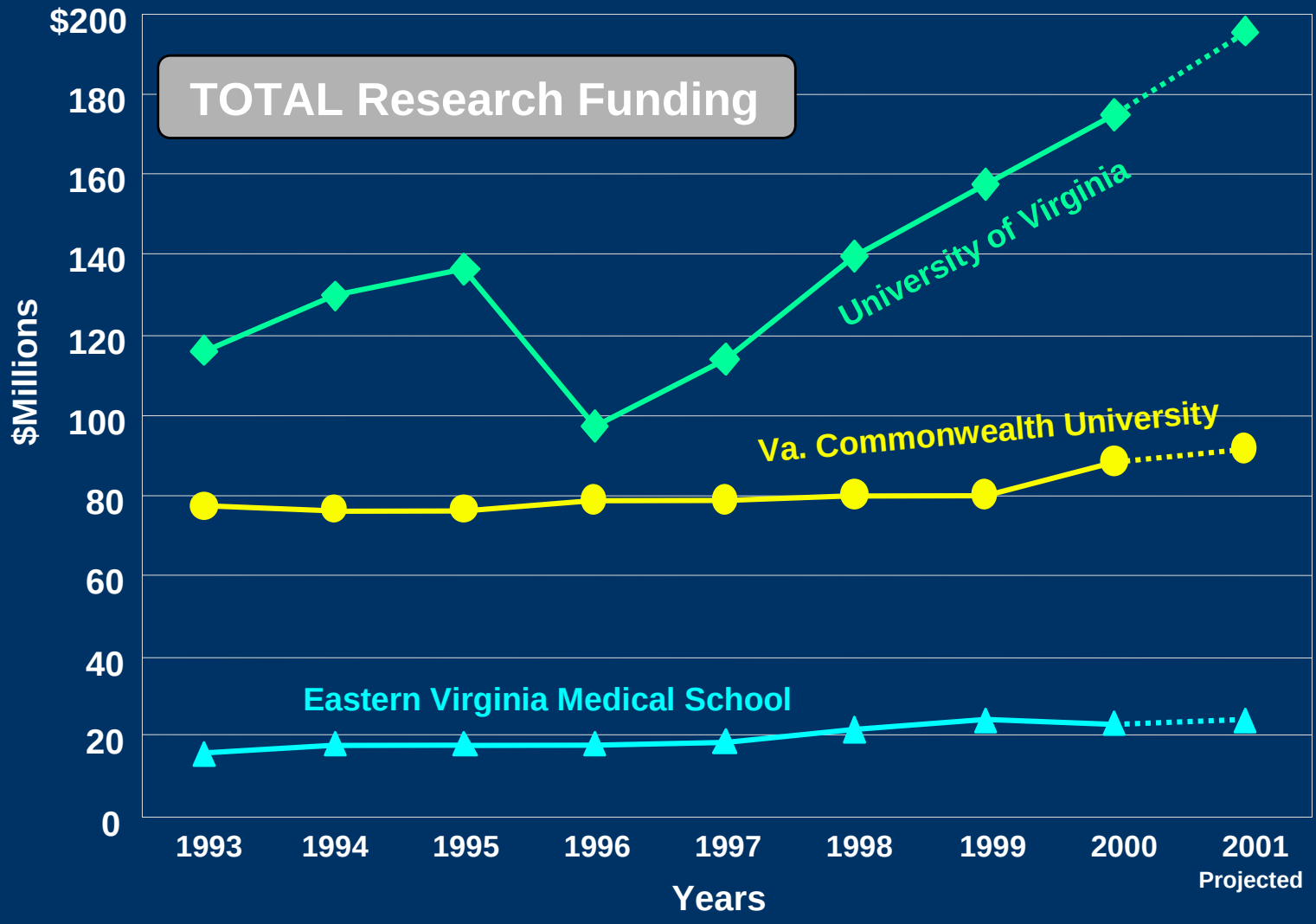
	Total Revenue for All Patients	Total Medicaid Payment	Total Indigent Care Payments
Virginia Commonwealth University (Medical College of Virginia)	$432.5	$87.7	$65.1
University of Virginia	$459.3	$63.4	$35.1
Eastern Virginia Medical School	$408.3	$36.0	$1.3

Medical Research Funding at Virginia's Medical Schools

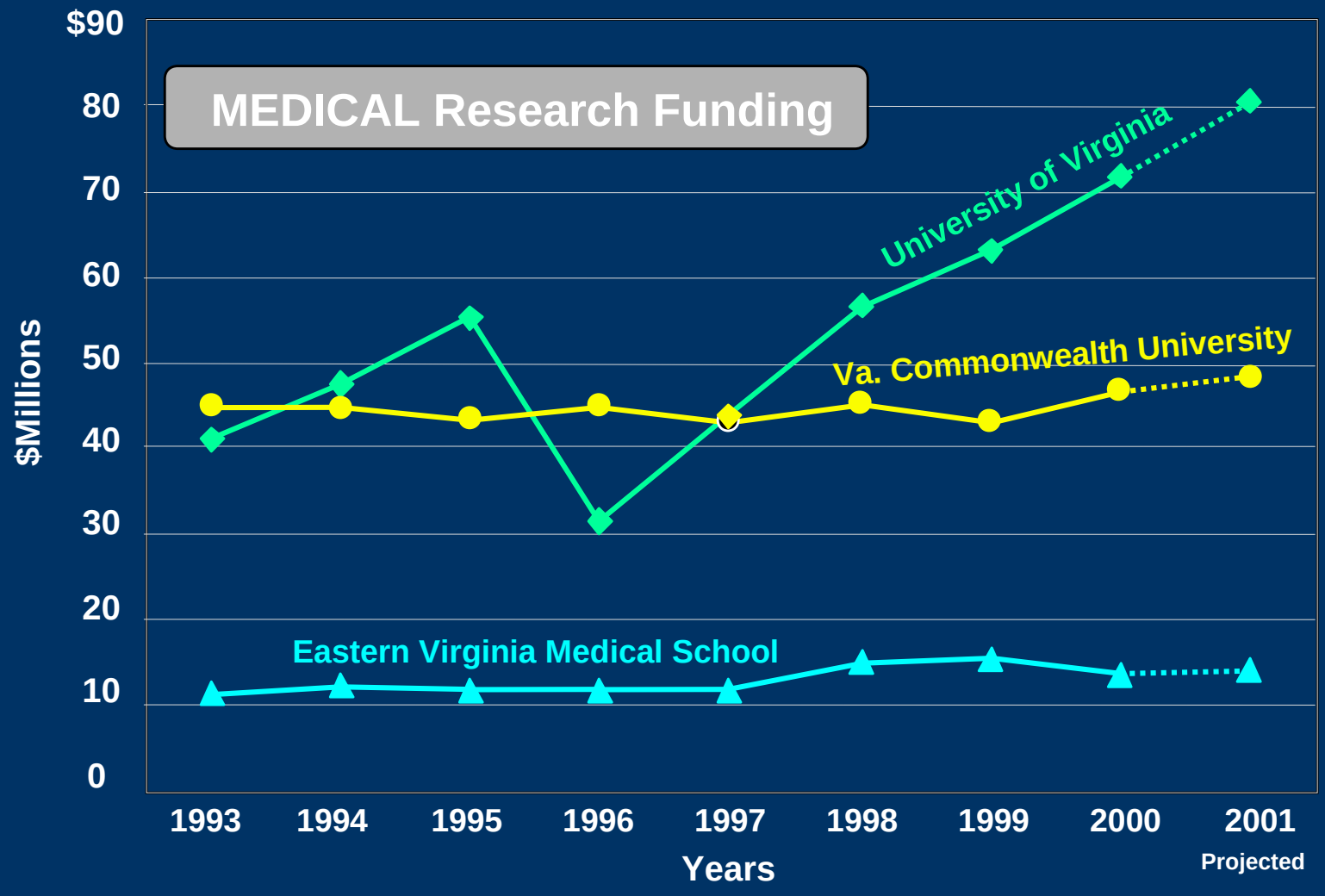
- VCU, UVA, and EVMS all have national reputations in conducting research, including medical research. For total research dollars in 1999, UVA was ranked 57th, VCU was ranked 107th, and EVMS was ranked 175th out of 589 schools nationwide.

- These schools are projected to receive over $311 million in total research funding and $143 million in medical research funding in 2001.
  - UVA's funding levels exceed the other schools, accounting for $195 million in total research funding and $80 million in medical research funding.

University Total Research Funding Trends,1993 - 2001



University Medical Research Funding Trends,1993 – 2001



Providing Health Care and Conducting Medical Research Are Separate Functions

- Providing health care to indigent persons and conducting medical research are two important, but largely separate, functions of each of Virginia's medical schools.
- However, because Virginia's medical schools are the main providers of indigent care, there is some concern that the willingness of indigent citizens to participate in a research study may be unduly influenced by the benefits of doing so, such as receiving health care services.
- In addition, a national concern is that the growth of medical research is outpacing the ability of universities to ensure the rights and welfare of human research participants.
- Therefore, this study examined whether the schools have strong internal oversight procedures in place to afford adequate protections for all Virginians who participate in medical research, including the most vulnerable and/or indigent citizens.

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Federal Audits of VCU Started with Participants' Complaints and a Routine Audit

- **The federal audits of VCU (by both FDA and OHRP) began in 1998 in response to study participants' complaints made directly to OHRP and a routine audit conducted by FDA.**
  - **A complaint was lodged against one longitudinal study by a father of twins who objected to sensitive questions included in a mailed questionnaire to his 20-year-old children.**
  - **A complaint about another study came from a participant who said that the study procedures for drawing blood from participants were changed without his consent**

VCU's Lack of a Prompt, Constructive Response Led to the Suspension of Research in Late 1999

- For sixteen months (from August 1998 to December 1999), communications went back and forth between VCU officials and federal officials before the federal agencies took punitive measures.
- Both FDA and OHRP's correspondence cited numerous administrative deficiencies, noncompliance with federal regulations concerning human subject protections, and potential psychological harm to the study participants who lodged the complaints.
- The suspension impacted 1,563 behavioral and medical research studies.

VCU Has Been Rebuilding Its University Research Oversight Program

- Beginning in January 2000, VCU hired an outside contractor to conduct its IRB activities while VCU staff completely redesigned its oversight program.
- The contractor had to re-review more than 1,500 behavioral and medical research studies and assume all IRB administrative functions. This review took more than a year and is still in progress.
- While VCU was able to resume research studies in the interim, the final phase of the federal suspension ended in March 2001.

VCU Made Changes in Response to Federal Suspension of Research

- Realigned IRB functions and increased resources (staffing, funding, and office space) for the IRB office.
- Improved human subject research materials and training for study investigators, IRB committee members and staff, and university officials. Developed a comprehensive IRB website.
- Rewrote IRB operating procedures to comply with federal regulations, including an Investigator's manual. Developed new standardized forms.
- Upgraded automated system for tracking research activities.
- Hired an outside contractor to re-review more than 1,500 behavioral and medical research studies and assume all IRB administrative functions.

The Suspension of Research Had a Significant Impact on the VCU Community

- Most study participants were not adversely affected because studies were allowed to continue when it was shown that it would be in the best interest of the subjects.
- VCU has incurred substantial one-time costs, including $1.6 million to pay for the services of an outside contractor.
- Some VCU students were unable to complete their degrees as planned.
- Some study investigators were unable to meet commitments to sponsors. VCU documented $14 million in research funds that were initially affected by the suspension.
- Several faculty reportedly left VCU because of the suspension.
- The suspension impacted the prestige of the university.

Federal Audits Were Also Conducted at UVA and EVMS

- Recent federal audits conducted at UVA and EVMS did not have the same negative impact as the VCU review because both schools were more responsive to federal concerns.
- Three federal compliance audits were conducted at UVA between 1994 and 1999. Each audit cited administrative deficiencies in UVA's IRB procedures; one audit resulted in a temporary suspension of 12 behavioral research studies. UVA corrected cited deficiencies promptly.
- In 1999, a FDA routine audit of EVMS found no significant deviations from federal regulations.

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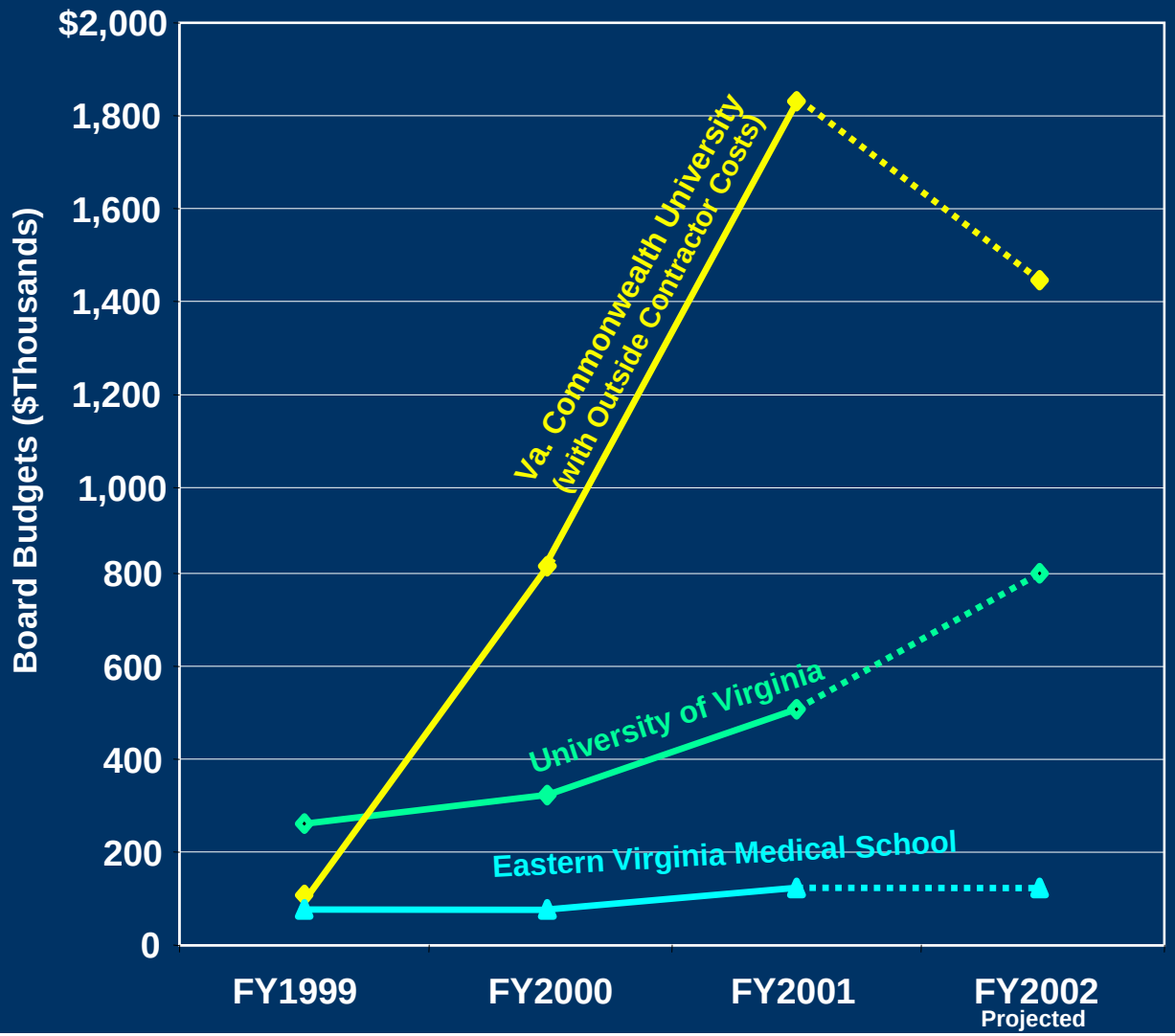
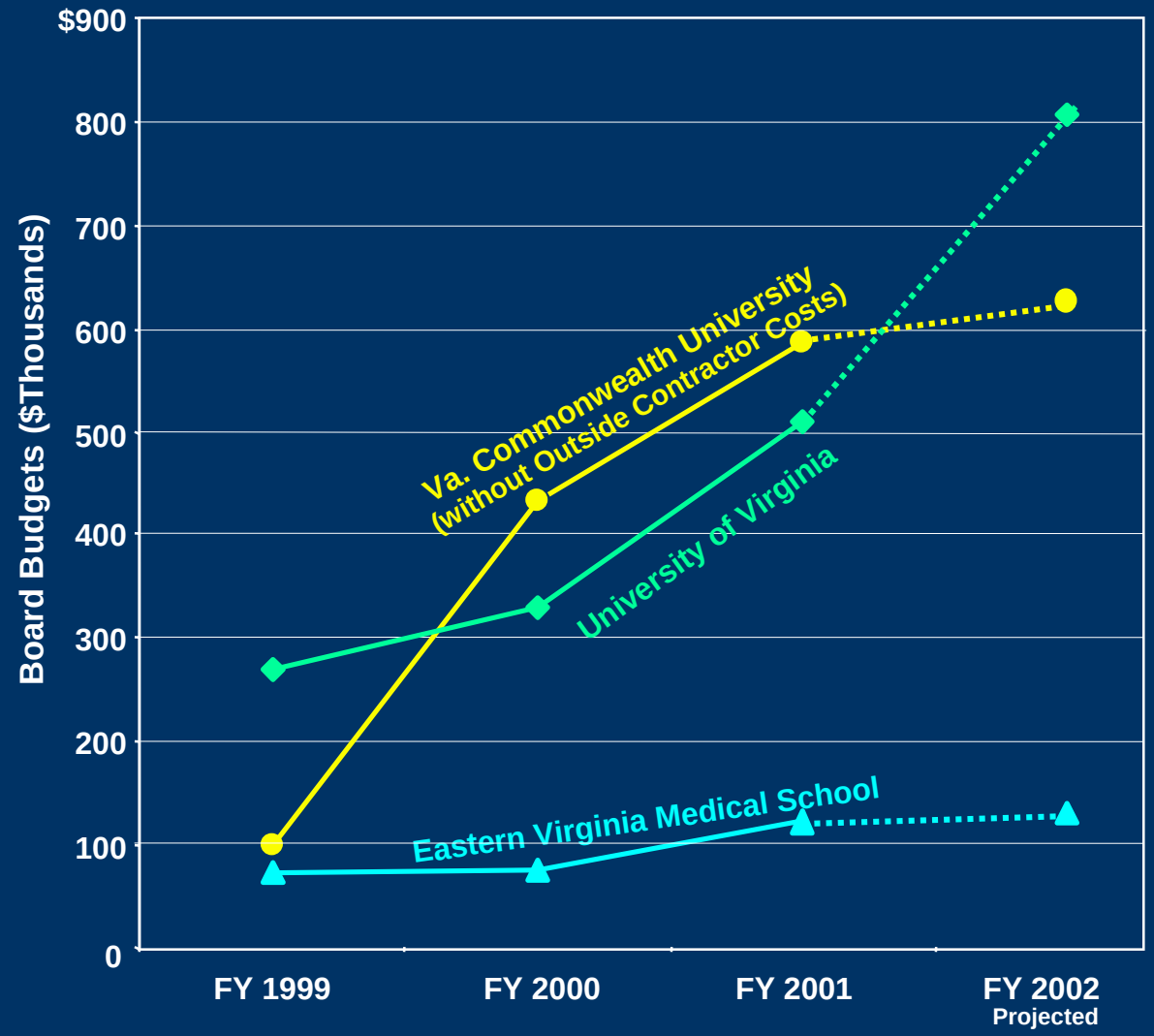
VCU Expenses Include One-Time Costs Due to the Suspension



Institutional Review Board Budgets Have Increased from 1999 to 2002



All Schools Have Improved Their Research Oversight Activities, But Additional Safeguards Are Needed

- As of March 2001, UVA was responsible for the oversight of 1,292 behavioral and medical studies, VCU was overseeing 1,263, and EVMS was overseeing 712 studies.
- In order to address how the schools are performing their oversight functions, JLARC staff reviewed several IRB oversight activities which were cited for non-compliance at one or more Virginia schools during past federal audits.
- Overall, JLARC staff found that no systemic problems currently exist at any of the schools, but additional safeguards are needed to protect potentially vulnerable populations.

Schools May Benefit by Reviewing the "Best Practices" of Other Schools

- The JLARC report compared all three school's IRB activities and procedures, and highlighted several "best practices" that appear to improve the administration or monitoring of human subject research.

- The best practices included: procedures for implementing the federal regulations (called standard operating procedures); procedures for providing standardized materials and improving the content and readability of consent forms; procedures for improving the education and training requirements; and procedures for conducting initial and continuing review of research studies.

Onsite Visits of Medical Research Studies Are Needed

- The IRB is charged with oversight of research studies at all stages. To more fully achieve this objective, however, it appears that IRB staff need to routinely visit selected medical research studies to ensure that study plans have not changed and that participant consents have been obtained properly.

- At the present time, only UVA conducts such audits on a limited basis. Both EVMS and VCU have audit plans under development.

Recommendation

- Each of the schools should improve the IRB procedures for continuing review of research studies by incorporating the best practices of other schools. At each school, the following activities should take place: (1) IRB members should routinely contact study investigators directly with any questions or concerns about the study under review; (2) IRB members should implement procedures to indicate when serious adverse event reports require follow-up reports; (3) IRB members should require more frequent progress reports for studies with a greater degree of risk to the study participants; and (4) IRB staff or an outside contractor should conduct routine onsite visits to selected studies, the priority for which should be tied to the assigned degree of risk and the frequency of study-sponsored reviews or other internal reviews.

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JLARC Staff Reviewed Selected Medical Research Studies and Found Problems

- Overall, the study investigators visited at the three schools appear to take their responsibility for safeguarding study participants seriously.
- However, each school had individual studies with problems that ranged from minor, isolated mistakes, to a few more serious study plan deviations.
- At VCU, one study investigator failed to re-consent study participants at their next visit as was required by the outside contractor. Another study investigator was unable to find one consent form, and a third investigator used an unapproved consent form.

JLARC Review of Medical Research Studies (continued)

- At UVA, one study investigator failed to obtain IRB approval prior to enrolling more subjects than had previously been approved, and another investigator improperly obtained an oral consent from a study participant.
- At EVMS, one study investigator failed to have consent forms witnessed despite the study plan explicitly stating this would be done.
- To improve compliance with federal regulations, a recommendation in the report states that the JLARC findings should be communicated to all study investigators.

Data Collection Procedures Are Needed to Ensure the Fair and Equitable Treatment of Vulnerable Groups, Including the Indigent

- In order to adequately safeguard all potential study participants, including vulnerable groups, JLARC staff found that each school must improve its ability to identify and monitor the participation of these groups in studies.
  - At the present time, no school collects basic demographic data on study participants or data on characteristics of potentially vulnerable groups throughout the study process.
- While the studies reviewed were not sufficient to draw broad conclusions on this point, it appeared that studies that served more potentially vulnerable populations (such as minorities or poor/uninsured) also had higher rates of consent errors.

Recommendation

- Each of the schools should implement data collection procedures to ensure the fair and equitable treatment of potentially vulnerable populations in research studies. The data should be submitted during the initial study application process (for those projected to serve), and updated in progress and close-out reports (to reflect the actual number served). Data collected, in aggregate form at the study level, should include basic demographic data (such as age, sex, and race), and data on the characteristics of the population which are related to the need for additional protections (for example, poor/uninsured subjects, or pregnant women).